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Proprotein convertase subtilisin/kexin 9 inhibitors in reducing cardiovascular outcomes: A systematic review and meta-analysis

Running title: PCSK9 inhibitors and CVD

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ABSTRACT

BACKGROUND

To evaluate the effects of proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors on major adverse cardiovascular events (MACE).

METHODS

Our systematic review included randomized controlled trials if they studied PCSK9 inhibitors in patients for primary and/or secondary prevention of cardiovascular diseases or with hypercholesterolemia/hyperlipidemia. Dichotomous variables from individual studies were pooled by relative risks (RR) and their 95% confidence intervals (CIs) using the random-effect model. Risk difference (RD) in the 10-year frame was also estimated using the pooled RR and the estimated baseline risk using the control group. Grading of Recommendation Assessment, Development, and Evaluation (GRADE) was used to assess the quality of evidence.

RESULTS

We included 54 trials with 97,910 patients in the analysis. Compared to controls, PCSK9 inhibitors significantly reduced the risk of MACE by 16% (RR, 0.84; 95%CI, 0.79~0.89; RD: 47 fewer per 1,000 versus 286 as the baseline risk; 95%CI, 32~59 fewer), nonfatal myocardial infarction (MI) by 17% (RR, 0.83; 95%CI, 0.74~0.93; RD, 35 fewer per 1,000 versus 207 as the baseline; 95%CI, 13~53 fewer), and any stroke by 25% (RR, 0.75; 95%CI, 0.65~0.85; RD, 16 fewer per 1,000 versus 61 as the baseline; 95%CI, 9~21 fewer) with moderate quality evidence. No significant differences were found between PCSK9 inhibitors and control groups in all-cause mortality, cardiovascular death, heart failure, or unstable angina with low-quality evidence.

CONCLUSIONS

This study demonstrated that PCSK9 inhibitors could significantly reduce the risk of MACE, nonfatal myocardial infarction (MI), and stroke.

KEYWORDS

Cardiovascular disease, low-density lipoprotein cholesterol, lipid-lowering drugs, proprotein convertase subtilisin/kexin type 9 inhibitors, systematic review

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors could lower the serum low-density lipoprotein (LDL) cholesterol level.

Several randomized controlled trials suggested some PCSK9 inhibitors, including alirocumab and evolocumab could reduce the risk of cardiovascular events.

WHAT DOES THIS STUDY ADD?

Our systematic review suggests PCSK9 inhibitors could significantly reduce the risk of major adverse cardiovascular events (MACE) by 16%, nonfatal myocardial infarction by 17%, and stroke by 25%.

The long-term effect of PCSK9 inhibitors needs further investigation in the real world practice.

HOW MIGHT THIS IMPACT ON CLINICAL PRACTICE?

Our study provides moderate-quality evidence for the clinical practice guideline that PCSK9 inhibitors reduce the risk of MACE, nonfatal myocardial infarction and stroke in patients for primary and/or secondary prevention of cardiovascular diseases or with hypercholesterolemia/hyperlipidemia.

INTRODUCTION

Lowering low-density lipoprotein (LDL) cholesterol to reduce the risk of cardiovascular disease (CVD) events is one of the cornerstones of both primary and secondary prevention.[1] There are several therapies available to lower LDL cholesterol, nevertheless, only statins have convincingly shown mortality and morbidity benefit on CVD events.[2] Of other previously available LDL-lowering agents, ezetimibe is the only one to have shown a marginal CVD outcome benefit, in selected patients[3]. Importantly however, despite the use of ezetimibe in addition to statin therapy, many patients fail to achieve their LDL cholesterol target,[4 5] and thus remain at elevated risk of CVD. Proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors are a new class of lipid-lowering drugs,[6] and the first drug in this class was approved for patients with familial hypercholesterolemia and CVD by the European Medicine Agency (EMA), the United States Food and Drug Administration (FDA), and the Canadian Agency for Drugs and Technologies in Health (CADTH) in 2015. Although this novel treatment strategy has been proven efficacious in reducing LDL cholesterol levels and improving lipid profile, whether this potentially translates to improved CVD outcomes using PCSK9 inhibitors remains uncertain in a different population.[7 8]

Upon the newly released clinical trials,[9-11] we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to determine the effect of PCSK9 inhibitors across all included populations of patients on the prevention of CVD.

METHODS

This meta-analysis followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement,[12] with the PRISMA checklist provided as **Tab S1** and was registered in PROSPERO (CRD42017073904).[13]

Data Sources and Searches

We searched MEDLINE (via OVID), EMBASE (via OVID), and Cochrane Central Register of Controlled Trials (CENTRAL, via OVID) from inception to 11 November, 2018 (the original data search was done on 24 July, 2017 and two updated searches were done on 10 August, 2018 and 11 November, 2018, respectively). Clinicaltrials.gov was screened for completed (with a label of “completed” or “terminated”) but not published registered trials **(Tab S2)**.

Study Selection

We included RCTs that compared PCSK9 inhibitors with placebo, standard care, or other active lipid-lowering agents in patients for primary and/or secondary prevention of cardiovascular diseases or with hypercholesterolemia/hyperlipidemia with at least one of our outcomes of interest, with no limitation to follow-up duration or blindness. Our primary outcome was major adverse cardiovascular events (MACE). The secondary outcomes included cardiovascular death, nonfatal myocardial infarction (MI), unstable angina, heart failure, any stroke, and all-cause mortality. For trials with duplicate or overlapping population, we included data from the article with the longest follow-up duration or the largest population.

Paired reviewers (HD, XL, NS, XH and HG) did the literature search and screened retrieved titles and abstracts of publications on the standardized way. The potentially eligible articles were retrieved for full-text and assessed by the paired reviewers (HD, XL, NS). Any discrepancies were discussed with the corresponding author (SL).

Study Data Extraction and Risk of Bias Assessment

Paired reviewers (HD, XL and NS) independently abstracted data from a standardized data collection template directed by a predefined protocol.[13] The primary outcome, MACE, was defined as a composite of cardiovascular death, nonfatal MI and nonfatal stroke. Where the definition of MACE in an included study is inconsistent with the above, we calculated the number of MACE by combining the number of patients of the three independent outcomes. The outcome definition of each secondary outcome was used in accordance with each included trial, while the unreported outcomes were calculated if available.

Paired reviewers (HD and NS) assessed the risk of bias and solved the disagreement by discussing with the corresponding author (SL) and a methodologist (LL). The risk of bias of all included trials was assessed by the Cochrane Risk of Bias Assessment Tool.[14]

Data Synthesis and Analysis

Dichotomous variables from individual studies were described as relative risks (RRs) and their 95% confidence intervals (CIs). We used the random-effects model to pool the data due to potential clinical heterogeneity. Statistical heterogeneity was examined by I^2 (inconsistency) and χ^2 test. The level of statistical heterogeneity was defined by p-value less than 0.10 in the χ^2 or I^2 more than 50%. The baseline risks and absolute risk changes for outcomes in a 10-year time frame were estimated using the pooled event rates in the control group and the pooled RRs and their 95% CIs, respectively. We also calculated the absolute risk difference of MACE based on the baseline risk of CVD being 10% and 20%, which were the cutoff of low to intermediate risk and intermediate to high risk regarding the Framingham Global Risk.[15] Three predefined subgroup analyses were undertaken based on the following hypotheses:

- Drug type (alirocumab, bococizumab, evolocumab, inclisiran, LY3015014 and RG7652; similar effect between drugs except for bococizumab, which was withdrawn due to safety concerns,[9 16] i.e. the class-specific rather than drug-specific effect)
- Follow-up duration (at least or less than one year / 48 weeks, larger effect in long-term observation)
- Prevention type (primary prevention, secondary prevention and unspecific, larger effect in the secondary prevention population). A trial was classified into the primary or secondary prevention if over 60% of its included population were in their primary or secondary prevention, respectively. If a trial was not in either of the two groups, it would be classified in the unspecific subgroup.

An exploratory subgroup analysis was also conducted based on the type of control group (placebo, non-placebo usual care and active lipid-lowering agents). The Grading of Recommendation Assessment, Development, and Evaluation (GRADE) framework was applied for rating the quality of evidence for each outcome in the pooled analyses and the quality of evidence was rated as high, moderate, low and very low quality.[17] The credibility of results from subgroup analyses was assessed by specific criteria.[18 19]

Funnel plots were conducted for visual symmetry to investigate publication bias when the total number of included studies surpasses ten, with Begg’s rank correlation test and Egger's linear regression approach performed subsequently. Predefined sensitivity analyses were conducted using different pooling methods (random-effects versus fixed-effects) and a leave-one-out approach. We also introduce two exploratory sensitivity analysis by excluding all bococizumab trials in the analysis of each study outcome and by excluding the studies adopting the calculated MACE in the meta-anlaysis of MACE, respectively. To assess the risk of type I and II errors, we conducted a trial sequential analysis (TSA) to calculate required information size (RIS) using the pooled RR of each outcome, 5% overall type I error and power of 80%.[20]

We managed the data analysis by Review Manager (Mac OS X, Version 5.3, Copenhagen), Stata (Version 14.2 for Mac, StataCorp, Texas), Trial Sequential Analysis Program (Version 0.9.5.10 beta, http://www.ctu.dk/tsa/), RStudio (Mac OS X, Version1.1.453), and GRADEprofiler (Version 3.6). Figures of subgroup analyses were prepared using DataGraph (Visual Data Tools, Inc. for Mac OS X, Version 4.3).

RESULTS

Trial Recruitment and Characteristics

Among 9,823 identified publications, 54 trials enrolling 51,627 patients receiving PCSK9 inhibitors and 46,283 controls were included in this meta-analysis. The flowchart is shown in **Fig 1**. The reasons for exclusion of the full-text screened papers was listed in **Tab S3**.

All included studies were multicenter clinical trials. Six PCSK9 inhibitors were investigated, including alirocumab (22 trials),[11 21-40] bococizumab (10 trials),[9 16 41 42] evolocumab (19 trials),[10 43-59]

inclisiran (1 trial),[60] LY3015014 (1 trial),[61] and RG7652 (1 trial).[62] Fifteen studies were phase II clinical trials and 39 were phase III (OSLER1/2 was a mixed trial of phase II and III.[57] ODYSSEY DM-DYSLIPIDEMIA was a mixed trial of phase IIIb/IV[39]). All studies were funded by pharmaceutical companies. The details of characteristics of the study are summarized in **Tab S4-S5**. The rationale of outcome data extraction and calculation were shown in **Tab S6**.

Risk of Bias Assessment

As shown in Figs S1-2, all studies adequately reported random sequence generation, allocation concealment, blinding of participants, and personnel. All but the open-label trials (ORION-1/2 and ODYSSEY DM-DYSLIPIDEMIA) clearly reported methods for blinding participants and personnel and for blinding outcome assessment. 51.8% of the trials were at high risk of incomplete outcome data because of over 10% of patients with missing data **(Tab S7)**. SPIRE trials were at high risk of other biases because of its premature termination due to the high rate of immunogenicity.[9 16] The ODYSSEY CHOICE I was also at high risk of other biases because of the imbalanced contamination of statin consumption.[35]

Meta-analysis of the Primary Outcome

As shown in **Fig 2**, 32 trials including 92,736 participants and 4,739 events reported MACE. The meta-analysis showed that PCSK9 inhibitors were associated with a significantly reduced risk of MACE (RR, 0.84; 95%CI, 0.79~0.89; P<0.00001). The absolute risk reduction of MACE was 47 (95%CI, 32~59) events per 1,000 patients in the 10-year time frame (the baseline risk in the control group was 286 per 1000). Using GRADE, we rated the quality of evidence in MACE as moderate by downgrading due to the indirectness of populations which varied across trials and were generally sparsely defined **(Tab 1)**. The TSA showed that the RIS of MACE was 20,820, which was achieved by the accrued study population, which confirmed that PCSK9 inhibitors could significantly lower the overall risk of MACE **(Figs S3-5)**.

As shown in **Figs 3-6**, none of the subgroup analyses showed significant heterogeneity across different drugs, trial designs, population and type of control (**Figs S4-7**), indicating the MACE reduction associated with PCSK9 inhibitors represents a class effect, regardless the follow-up duration, study population or control agents.

Sensitivity analyses using the fixed-effect model, the leave-one-out assay and the pooled analyses excluding bococizumab trials confirmed the robustness of the results **(Figs S8-110)**. The Begg's funnel plot and test and Egger's test did not indicate a significant publication bias **(Figs S121-13, Tab S8)**.

Meta-analyses of Secondary Outcomes

As shown in **Figs 3-6**, PCSK9 inhibitors significantly reduced the risk of nonfatal MI (RR, 0.83; 95%CI, 0.74~0.93; P=0.0008, **Fig S14**) and any stroke (RR, 0.75; 95%CI, 0.65~0.85; P<0.0001, **Fig S15**). The absolute risk reduction of nonfatal MI and any stroke were 35 (95%CI, 13~53) and 16 (95%CI, 9~21) events per 1,000 patients versus 207 and 61 as the baseline in the control group in the 10-year time frame, respectively. The quality of evidence for both outcomes was rated as moderate, due to the indirectness (**Tab 1**). The TSA also confirmed the results with the cumulative Z curves of both outcomes surpassing the conventional boundary and trial sequential monitoring boundary (**Figs S16-17**).

Subgroup analyses indicated that PCSK9 inhibitors further reduced the risk of nonfatal MI in trials with longer follow-up duration comparing with those shorter (at least one year: RR, 0.79; 95%CI, 0.69~0.91 and less than one year: RR, 1.11; 95%CI, 0.84~1.46; interaction P = 0.03, **Fig 4 and Fig S18**). However, we judged the credibility of this subgroup effect to be low, because it was inconsistent with other associated subgroups, free of indirect evidence to support, neither a baseline characteristic nor stratification factor at randomization.[19] None of the other subgroup analyses showed any evidence for the significant interaction across different drugs, trial design and population (**Figs S19-25).**

As shown in F**igs 3-6 and Figs S26-29**, no significant differences were found for all-cause mortality (RR, 0.93; 95%CI, 0.84~1.03), cardiovascular death (RR, 0.95; 95%CI, 0.85~1.07), unstable angina (RR, 0.90; 95%CI, 0.78~1.04) or heart failure (RR, 0.96; 95%CI, 0.83~1.1). With no cumulative Z curve crossing the conventional or the trial sequential monitoring boundary, the TSA suggested that the current sample evidence is insufficient to conclude the effect of PCSK9 inhibitors in unstable angina outcome. The quality of evidence for these four secondary outcomes was rated as low, rated down due to the indirectness and imprecision, caused by insufficient sample size calculated by TSA **(Tab 1)**. In subgroup analyses, no significant difference was found across different subgroups. Detailed subgroup analyses and TSA are shown in **Figs S30-45, Figs S46-49,** respectively.

The leave-one-out sensitivity analyses identified that the FOURIER trial may change the pooled results of unstable angina, heart failure and all-cause mortality, while the ODYSSEY OUTCOMES trial may affect the results of cardiovascular death and all-cause mortality. The sensitivity analyses using the fixed-effects model and excluding bococizumab trials showed the robustness of the results (**Figs S50-55 and Figs S56-61, Figs S62-67**). Publication bias was not detected by the tests (**Figs S68-79, Tab S8)**.

DISCUSSION

This meta-analysis, including 54 RCTs with 97,910 patients, demonstrated that PCSK9 inhibitors could reduce the relative risk of MACE by 16%, of any stroke events by 25%, and of nonfatal MI by 17%, with moderate

quality evidence as assessed by GRADE and with confirmation using both sensitivity analyses and TSA. The subgroup analyses showed consistency across different drugs, follow-up durations and populations in MACE and stroke. PCSK9 inhibitors could potentially reduce nonfatal MI with greater relative effect in trials with longer follow-up duration. These findings demonstrated that PCSK9 inhibitors could be used in reducing the risk of cardiovascular diseases and consistent with previously published meta-analyses **(Tab S9)**.

Clinical Interpretation

According to current the United Kingdom guidelines, statins are recommended in patients with a 10% or greater 10-year CVD risk for the primary prevention and all patients with established diagnosis of CVD for the secondary prevention.[63] If the LDL cholesterol levels are not reduced to the recommended target (4mmol/L for patients with high risk of CVD and 3.5mmol/L for very high risk, respectively) or the patients are intolerant to statins, second-line agents such as ezetimibe and PCSK9 inhibitors should be considered. Our study provided moderate quality evidence that PCSK9 inhibitors probably reduce an overall 47 events of MACE per 1,000 in patients with 20% baseline 10-year CVD risk in a 10-year period. This was predominantly driven by significant reductions in nonfatal MI and stroke, with a small, non-significant reduction in mortality. Our study also showed a nonsignificant trend of reducing unstable angina events by PCSK9 inhibitors, the direction of which was consistent with other related outcomes in the study. However, the TSA suggested further trials with the larger population was required to confirm the effect.

The absolute effects on CVD depend on the baseline cardiovascular risk of the populations. The baseline risk of MACE in the control group population was 29%, which reflected high-risk patients, suggesting guideline developers and others making use of our results should carefully assess the anticipated benefits of PCSK9-inhibitors in broad populations of patients, likely to be at lower risk of future cardiovascular events. Nevertheless, these results support the use of PCSK9 inhibitors in addition to statins in patients not yet at target LDL cholesterol levels, suggesting 32 and 16 events of MACE could be prevented per 1,000 patient-10-year in the population with baseline CVD risk of 20% and 10% in 10 years, respectively. Following the results of the trials, both European and American guideline committees have immediately released updated guidance recommending the use of PCSK9 inhibitors in addition to maximally tolerated statin therapy (with or without ezetimibe) in those patients who have not met their LDL cholesterol-target.[7 8 64 65]

Importantly, while we have evidence supporting the use of evolocumab and alirocumab for reduction of CVD, the terminated SPIRE series trials of bococizumab highlighted a potential safety issue of high-titer antibodies against the agent.[9 16] Although the recent evidence – according to systematic reviews – did not show the risk of developing drug antibodies, elevated creatine kinase, diabetes or overall serious adverse events in other PCSK9 inhibitors,[10 21 66-68] a signal of increased risk of neurocognitive adverse events was

observed in a subgroup analysis of a systematic review,[67] which is conflicted with another systematic review.[69] We propose long-term monitoring of neurocognitive function and other adverse events in the real world practice to confirm the apparent safety of these novel drugs. The high price of PCSK9 inhibitors (£340.2 versus £26.31 for 28-day evolocumab and ezetimibe in the UK, respectively) is also a concern in clinical practice.[70] A just-in-time cost-effectiveness analysis based on the ODYSSEY OUTCOMES trial suggested that the price of alirocumab should be reduced to be reasonable in the US health system.[71] The latest American guideline suggested the low to the intermediate economic value of PCSK9 inhibitors could be a major concern in the clinical interpretation.[65]

Strengths and Limitations

The strength of our study is the capture of the entire body of published evidence, with the added value of including all levels of the population including primary and secondary prevention of CVD. Secondly, we exclusively focused on six predefined cardiovascular outcomes and all-cause mortality with rigorous approaches, including systematic and transparent critical appraisal with GRADE. Thirdly, the statistical reliability was confirmed by TSA and the robustness of the results by the sensitivity analyses.

Our study also has limitations. Firstly, we included studies with patients receiving all levels of prevention for CVD, which raises concerns about the applicability of results from the meta-analysis across populations. However, we conducted subgroup analyses to explore the source of heterogeneity and sensitivity analyses to test the robustness of results. Despite the absence of credible subgroup effects across primary and secondary prevention, we took a conservative approach and rated the quality of evidence as moderate due to indirectness. This judgment was informed by the characteristic of included patients. These patients were at high risk of CVD and not necessarily representative of patients in all clinical settings when used for the development of guidelines. Secondly, the most extended follow-up duration in the included trials was no more than three years, which limited our ability to explore the effect of life-long cardiovascular prevention. Thirdly, we did not obtain individual data for each trial, which might have resulted in more valuable data for subgroup analysis. Finally, we did not include adverse events in our systematic review, signaling a need for updated systematic reviews to fully inform clinicians and patients in decision-making, for example through clinical practice guidelines.

CONCLUSIONS

In conclusion, our systematic review and meta-analysis demonstrated that PCSK9 inhibitors reduce the risk of MACE, nonfatal MI and stroke. However, pragmatic trials and well-designed observational studies with longer

follow-up duration and larger sample size are warranted to further investigate the long-term effect of PCSK9 inhibitors in the real-world practice.

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Contributorship Statement

HT, JL and SL planned this study. HD, XL, NS, XH, HG performed the literature search and screening. HD, XL and NS extracted the study data. HD and NS performed the risk of bias assessment. HD, LL and LZ performed the statistical analyses. JSK, POV and XY provided critical comments in methodology and revised the manuscript. IRM, LR and CCL provided critical comments in clinical cardiology. HD, XL, IN, IRM and SL drafted the manuscript. All authors critically reviewed the manuscript and participated in the interpretation of the results. SL is responsible for the overall content as the guarantor.

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Competing interests

None reported.

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FIGURE LEGENDS

Figure 1. Flow diagram for study identification and inclusion (PRISMA Flow Diagram).

* These 47 citations included 55 randomized trials.

Figure 2. Effect of PCSK9 inhibitors on MACE

Abbreviations: CI, confidence interval; MACE, major adverse cardiovascular events; RR, relative ratio; PCSK9, proprotein convertase subtilisin/kexin type 9; M-H, Mantel-Haenszel.

Figure 3. Subgroup analyses based on the drug type

Abbreviations: CI, confidence interval; PCSK9, proprotein convertase subtilisin/kexin type 9.

Figure 4. Subgroup analyses based on the follow-up duration.

Abbreviations: CI, confidence interval; PCSK9, proprotein convertase subtilisin/kexin type 9.

Figure 5. Subgroup analyses based on the prevention type.

Abbreviations: CI, confidence interval; PCSK9, proprotein convertase subtilisin/kexin type 9.

Figure 6. Subgroup analyses based on the control type.

Abbreviations: CI, confidence interval; PCSK9, proprotein convertase subtilisin/kexin type 9.

TABLE LEGEND

Table 1. GRADE quality assessment

[a] Indirectness of populations which varied across trials and were generally sparsely defined

[b] The baseline risk in a 10-year time frame was estimated using the pooled event rates in the control group

[c] The cutoff between the intermediate and high risk of CVD in FGR

[d] The cutoff between the low and intermediate risk of CVD in FGR

[e] Cumulative Z line crossed futility boundary in the trial sequential analysis

[f] Cumulative Z curve did not cross futility boundary, trial sequential monitoring boundary, traditionary boundary

Abbreviations: CI: confidence interval; CVD: cardiovascular disease; FGR: Framingham Globe Risk; GRADE: Grading of Recommendation Assessment, Development, and Evaluation; MACE: major adverse cardiovascular events; PCSK9: proprotein convertase subtilisin/kexin 9; RR: relative risk.

Table 1. GRADE quality assessment

Quality assessment							No of patients		Relative effect (95% CI)	Anticipated absolute effects (10-year time frame)		Quality
No of participants (studies)	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCSK9 inhibitors	Control		Baseline risk of CVD	Risk difference with PCSK9 inhibitors[1] (95% CI)	
MACE (follow-up 12-145.6 weeks)												
92,736 (32)	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[a]	No serious imprecision	None	2,188/48,518 (4.5%)	2,551/44,218 (5.8%)	RR 0.84 (0.79 to 0.89)	Risk in the control[b]		MODERATE
										286 per 1,000	47 fewer per 1,000 (32 to 59 fewer)	
										Intermediate to high risk in FGR[c]		
										200 per 1,000	32 fewer per 1,000 (22 to 42 fewer)	
										Low to intermediate risk in FGR[d]		
										100 per 1,000	16 fewer per 1,000 (11 to 21 fewer)	
Cardiovascular Death (follow-up 12-145.6 weeks)												
96,709 (51)	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[a]	Serious[e]	None	585/50,914 (1.1%)	600/45,795 (1.3%)	RR 0.95 (0.85 to 1.07)	65 per 1,000[2]	3 fewer per 1,000 (10 fewer to 4 more)	LOW
Nonfatal Myocardial Infarction (follow-up 12-145.6 weeks)												
90,605 (38)	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[a]	No serious imprecision	None	1,341/47,031 (2.9%)	1,602/43,574 (3.7%)	RR 0.83 (0.74 to 0.93)	207 per 1,000[2]	35 fewer per 1,000 (15 to 53 fewer)	MODERATE
Unstable Angina (follow-up 12-145.6 weeks)												
93,344 (36)	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[a]	Serious[f]	None	371/48,877 (0.8%)	400/44,467 (0.9%)	RR 0.9 (0.78 to 1.04)	54 per 1,000[2]	5 fewer per 1,000 (12 fewer to 2 more)	LOW
Heart Failure (follow-up 12-145.6 weeks)												
92995 (34)	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[a]	Serious[e]	None	388/48,673 (0.8%)	395/44,322 (0.9%)	RR 0.96 (0.83 to 1.10)	43 per 1,000[2]	2 fewer per 1,000 (7 fewer to 4 more)	LOW
Any Stroke (follow-up 12-145.6 weeks)												
94,408 (35)	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[a]	No serious imprecision	None	393/49,537 (0.8%)	512/44,871 (1.1%)	RR 0.75 (0.65 to 0.85)	61 per 1,000[2]	16 fewer per 1,000 (9 to 21 fewer)	MODERATE
All-cause Mortality (follow-up 12-145.6 weeks)												
96,427 (51)	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[a]	Serious[e]	None	941/50,888 (1.8%)	980/45,539 (2.1%)	RR 0.93 (0.84 to 1.03)	113 per 1,000[2]	8 fewer per 1,000 (19 fewer to 3 more)	LOW

a Indirectness of populations which varied across trials and were generally sparsely defined

b The baseline risk in a 10-year time frame was estimated using the pooled event rates in the control group

c The cutoff between the intermediate and high risk of CVD in FGR

d The cutoff between the low and intermediate risk of CVD in FGR

e Cumulative Z line crossed futility boundary in the trial sequential analysis

f Cumulative Z curve did not cross futility boundary, trial sequential monitoring boundary, traditionary boundary

Abbreviations: CI: confidence interval; CVD: cardiovascular disease; FGR: Framingham Globe Risk; GRADE: Grading of Recommendation Assessment, Development, and Evaluation; MACE: major adverse cardiovascular events; PCSK9: proprotein convertase subtilisin/kexin 9; RR: relative risk